REMARKS

Claims 1-4, 7, 8, 12, 26-28, 30-35, 38-45, 47-50, 53-59, 61 and 63-74 were pending in this application at the time the outstanding Office Action was issued. Claims 26-35, 38-50, 53-61, 63-68 and 70-72 previously were withdrawn from consideration as a result of the examiner's decision regarding the restriction requirement and now have been canceled. Claims 1-4, 7, 8, 12, 69, 73 and 74 are under examination and have been rejected. By amendment above, Applicants have added claims 75 and 76 to this application. These two new claims are dependent, directly or indirectly, from claim 1, and merely identify the cationic and neutral or helper lipids of the cationic liposome component of the claimed immunoliposome complex. Support for these claims is clearly found in example 3 and including these claims with those already being examined does not place a further burden on the examiner.

Claims 7 and 8 have been rejected under 35 U.S.C. §112, second paragraph as being indefinite. These rejections have been obviated by the amendments above to these two claims which correct their claim dependencies.

Claims 1-3, 7, 12, 73 and 74 have been rejected under 35U.S.C. §103 (a) as unpatentable over a reference by Yu et al. in view of references by Wang et al, Nilsson et al. and Martin et al. The primary reference was said to teach that liposome-mediated gene transfer significantly inhibited the growth and dissemination of ovarian cancer cells that over express HER-2/neu in treated mice and using a DNA:liposome ratio of 1:13 which is within the range recited in claim 1 of the present application. Yu

et al. further were said to teach that liposomes can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor. The examiner noted that Yu et al. did not teach the method or ratio of incorporation of an scFv antibody fragment into liposomes by direct conjugation via a sulfur atom that was a part of a sulfhydryl group at a carboxy terminus on the scFv. Wang et al. were said to teach the generation of an scFv with anti-CD19 specificity that can be linked with a toxin through a disulfide bond such that the toxin can be targeted to CD19-expressing B cell lymphomas and leukemias and that using an scFv was advantageous over the use of a full antibody. Nilsson et al. were said to teach targeting drugs to a specific cell type using monoclonal antibodies and that scFv fragments have the same affinity as the corresponding full-length antibody. Martin et al. were cited as teaching the coupling of immunoglobulin Fab' fragments to liposomes to provide improved coupling efficiencies and stable linkages. The examiner asserted that it would have been obvious to have made an scFv antibody fragment as taught by Nilsson et al. with a carboxy terminal cysteine residue such as taught by Wang et al. having the specificity taught by Yu et al. and to have coupled it to the cationic immunoliposome directly via use of MPB to utilize conjugation through the sulfur atom on the scFv-cys. This rejection is traversed.

The primary reference relied upon by the examiner in making this rejection is the paper by Yu et al. in which they report that cationic liposomes were used to directly deliver the EIA gene into adenocarcinomas in mice and that the liposome-mediated EIA

gene transfer was found to significantly inhibit growth and dissemination of ovarian cancer cells that over-express HER-2/neu. The examiner asserted that the reference teaches that the liposomes can be targeted to tumors that overexpress p185 by incorporating into the liposomes anti-p185 antibodies against the HER-2/neu-encoded p185 receptor. The examiner acknowledged that the paper does not teach "the method nor ratio of incorporation of antibody that is an scFv into liposomes by direct conjugation via a sulfur atom that was a part of a sulfhydryl group at a carboxy terminus on the scFv."

Not only does the Yu et al. paper not teach the method or ratio of incorporation of an scFv antibody fragment into liposomes, it does not teach even the general concept of incorporation of antibodies into liposomes, Yu et al. did not use an antibody, much less an scFv antibody fragment, to target liposomes to tumors. The authors have targeted the E1A gene to the HER-2/neu gene inside the tumor cell; they did not target a DNA-liposome by an antibody to p185 protein. This reference, therefore, is not relevant to the present invention. Yu et al. do not teach that liposomes can be targeted to tumors that over-express an antigen, such as p185, by incorporating antibodies, such as anti-p185 antibodies, into the liposomes.

The examiner cited a paragraph on page 1385 of the reference which provides the ratio of DNA to liposome; as the authors did not use a ligand they do not suggest a suitable ratio of a ligand to the liposome. The examiner also cited a paragraph on page 1387 of the reference. In this paragraph the authors note that a future effort should be

"designing liposomes that can target the E1A gene to tumors that overexpress p185 by incorporating into liposomes anti-p185 antibodies or the ligand for the HER-2/neu-encoded p185 receptor (when it becomes available)." This does no more than suggest that incorporating antibodies into liposomes could be tried; no such immunoliposomes have been made and there is no guidance provided as to how one would make the immunoliposomes, the ratios of target nucleic acid to antibody or nucleic acid and antibody to liposome, that scFv antibody fragments could be used rather than intact antibodies or how the antibody or antibody fragment would be conjugated to the liposome.

The cited secondary references do not compensate for the shortcomings of the primary Yu et al. reference. Wang et al. were cited as teaching the linking of an scFv with anti-CD19 specificity with a carboxy terminal cysteine to a toxin through a disulfide group and using the resultant complex to target the toxin to CD19-expressing B cell lymphomas and leukemias. The primary shortcoming of this reference was noted by the examiner in his description of it–this paper does not teach or suggest directly binding an scFv to a liposome. The paper does not teach or suggest how one could link an scFv to anything other than a protein, and it is not obvious from the teachings of this paper that one could link an scFv with a cysteine to a liposome.

Wang et al. teach using a molar ratio of scFv to toxin as 1:1 - 1:2. Claim 1 of the present application provides for a wt:wt ratio (expressed in μg) of scFv to liposome of

1:5 - 1:40. Based on *Molecular Cloning: a Laboratory Manual*, 3rd edition, by Sambrook and Russell, Cold Spring Harbor Press, 2001, for a 28 kDa protein (i.e. an scFv),

1 µg of scFv is 0.036 nmol

1 mg is the equivalent to 36 nmol

Based upon its molecular weight,

1 µg of liposome is equivalent to 1.4 nmol

5 µg of liposome thus is equivalent to 7 nmol

40 µg of liposome thus is equivalent to 56 nmol

Therefore, the wt : wt (µg) ratios of scFv : liposome in claim 1 of the application of

1 µg : 5 µg - 1 µg : 40 µg

has a corresponding molar ratio of

0.036 nmol : 7 nmol - 0.036 nmol : 56 nmol

or which is the same as a molar ratio of

1 : 194.4 - 1 : 1555.6 (scFv : liposome)

Thus, the molar ratio required in claim 1 for complexing an scFv to a liposome such that the resulting complex will have the desired biological activity clearly is not comparable to the 1:1 - 1:2 molar ratio taught by Wang et al. for binding an scFv to a liposome. The difference is significant, and extensive experimentation would be required, with no guidance provided from Wang et al., to reach the claimed ratio if one were to start with the ratios advocated by Wang et al.

There are further shortcomings to the Wang et al. paper. Wang et al. teach that the maximum yield of scFv -toxin at 1 : 1 was 70% incorporation (see page 881, first full paragraph). When they increased the ratio to 1 : 2, the percent of complex decreased to only 40%. In view of these teachings, one of skill in the art would have found it to be highly unexpected that the Applicants' ratio of 1 : 194 - 1:1556 would be usable and result in a minimum of 90 - 95% incorporation (as reported in the declaration by Dr. Esther Chang provided in response to the previous Office Action). This illustrates the significant difference between linking an antibody fragment to a protein, such as a toxin, and to a liposome, and the fact that the former could be done does not lead one to expect that the latter also could be accomplished. Certainly there is nothing in this paper that would make the linking of an antibody fragment to a liposome obvious.

Furthermore, on page 881, last paragraph, Wang et al. state that the scFv-toxin was 100 fold less potent than the complete antibody-toxin (the IC_{50} for the scFv-toxin was 1 - 1.3 x 10^{-9} , while the IC_{50} for the full AB-toxin was 2-3 x 10^{-11}). These differences are quite significant–and indicate that the scFv was not superior to the full antibody even though the addition of the cysteine did not interfere with its antigen binding capacity. These results, as well as the results Wang et al. reported of the negative affect on yield when going from a 1:1 to 1:2 molar ratio of scFv to toxin, teach away from the present invention.

The examiner specifically noted the first sentence of the last paragraph on page 883 of the Wang et al. paper, in which the authors state that "the formation of a

disulfide-linked protein is an effective approach to produce anti-CD19 scFv immunotoxin." Applicants respectfully submit that the key word here is "immunotoxin;" the authors do not assert that their approach would produce an effective immunoliposome. Furthermore, as noted above, this immunotoxin comprising the scFv was less potent than the immunotoxin with the full antibody.

It also should be noted that the Wang et al. paper also points out the criticality of refolding in the preparation of the scFv (see the paragraph bridging pages 881 and 882). They further indicate that using their method of preparation, the yield of properly refolded scFv is low (only 0.5 - 1 mg/L)–and that this fact "may limit the large scale production of FSV191cys-dgRTA." This admission shows the limited usefulness of the Wang et al. construct, and would not lead one of skill in the art to try to use scFv with liposomes. Thus, there is nothing in the teachings of this reference to suggest the immunoliposomes of the present invention.

The second of the secondary references relied upon by the examiner is the paper by Nilsson et al. This paper is a review article which discusses fusion proteins in general, covering a wide range of proteins and not scFv specifically (see Table 2). And, as noted by the examiner on page 3 of the Office Action, what is discussed is the use of whole monoclonal antibodies to target drugs, not scFv to target DNA. The use of scFv is not discussed in this context.

As noted above, the focus of the paper is on fusion proteins. Nilsson et al. do not teach how one would use a molecule, such as an scFv-cys, that is not a fusion

protein, to link to a liposome. There is no discussion in the paper of using an scFv with a liposome or of using an scFv for targeted delivery (the only reference is to the use of whole antibodies for delivery; see the discussion on page 572 on "Protein Drug Targeting") and no discussion of conjugating an scFv to a liposome through a sulfur atom which is part of a cysteine residue. Thus, this paper is not relevant to the present invention.

The final secondary reference relied upon by the examiner is a paper by Martin et al. which had been cited by the examiner in the previous Office Action. As Applicants noted in their response to that Action, the Martin et al. paper is not relevant to the present invention, as the authors focus on the coupling of Fab' fragments, not scFv, to liposomes. Martin et al. make no suggestion of scFv-liposome complexes. As Applicants previous have noted, an Fab' is quite distinct from an scFv. The two fragments have different structures and sizes and different behaviors and uses.

Martin et al. do not give any guidance as to what ratio one would use with an scFv rather than an Fab. This lack of guidance is significant, especially because of the difference in size of the two types of fragments (Fab are about 55-60 kDa; scFv are approximately 24-28 kDa). One of skill in the art would not expect to be able to simply replace one type of fragment for the other.

The examiner asserted that Martin et al. teach the coupling of antibody fragments to liposomes at a ratio of 250 µg Fab' fragments to 1-2 µmol of liposome, a wt:wt ratio of about 1:24 - 1:48, or 1.4 µmol/ml lipid to Fab' at 0.5-4.0 mg/ml, a wt:wt

ratio of about 1:14 - 1:2 protein to lipid. This is a misstatement of what Martin et al. teach. First, the 250 µg of Fab' is the amount of the complex of Fab' coupled to lipid vesicles used in a time course study (fig. 3, page 287), not the ratio of Fab' to phospholipids used to make the complex. Furthermore, although the examiner asserted on page 5 of the Office Action that the wt:wt ratios taught by Martin fall within the range in the present claims, Applicants respectfully submit that the ratios are, in fact, very different, as shown below:

From page 286, column 2, 3rd full paragraph, and page 287, column 1, second full paragraph, of the Martin et al. paper, the ratio used to make the complexes with the Fab is

0.5 to 4 mg Fab to 1-2 µmol vesicles

Based upon the ratios of the three lipids used to compose the vesicles, 10:9.5:0.5 (cholesterol:PC:MPB-PE) and their published molecular weights (386.7, 760.1 and 956.2, respectively), 1 µmol of the vesicle is equivalent to 0.58 µg:

cholesterol 1µM = 386.7 µg/µl x 10 = 3.9 mg

PC 1µM = 760.1 µg/µl x 9.5 = 7.2 mg

MPB-PE 1µM = 478.1 µg/µl x 0.5 = 0.5 mg

Thus, 20 µmol = 11.6 mg (20 µmol is selected in view of the ratio of the three lipids (10 + 9.5 + 0.5) and

1 µmol = 0.58 mg;

2 μmol = 1.16 mg.

1.4 μmol = 0.81 mg (1.4 μmol is the specific amount within the 1-2 μmol range used in the experiment described in the second full paragraph on page 287 of the Martin et al. paper)

Therefore, Martin et al.'s w/w ratio range of Fab to vesicles (0.5 to 4 mg/ 1-2 μmol) is equivalent to:

0.5 mg/1 μmol = 0.5 mg/0.58 mg, or 1 : 1.16

4.0 mg/1 μmol = 4.0 mg/0.58 mg, or 1 : 0.145

to

0.5 mg/2 μmol = 0.5 mg/1.16 mg, or 1 : 2.32

4.0 mg/2 μmol = 4.0 mg/1.16 mg, or 1 : 0.29

Thus, their ratio range is significantly outside the w/w ratio range (1:5 to 1:40) given in the claims of the present application. Contrary to the examiner's assertion, therefore, Martin et al. thus do not teach how to use scFv. It would take a significant amount of experimentation to go from the ratios useful for Fab' to those useful for scFv, and Martin et al. provide no guidance for that experimentation. Thus, simply because one can use Fab' with liposomes does not make it obvious that one could use scFv.

Applicants note that they addressed this difference in ratios in a slightly different manner in their response to the preceding Office Action. In that response, Applicants

used a single lipid concentration of 1.4 μmol/ml used in the experiment described on page 287 of the Martin et al. paper, rather than the broader range of 1-2 μmol/ml provided in the broader "Materials and Methods" section of the paper and used in the calculations above. Furthermore, in making their comparison in the previous response, applicants converted the wt:wt ratio set forth in claim 1 to the wt/mole format used by Martin et al. On page 5 of the present Action, the examiner dismissed that comparison on the basis that the present claims "do not recite a weight to umol ratio" and the weight to weight ratios taught by Martin et al. fall within the range recited in the present claims. Whether one converts the wt:wt ratio of the present claim 1 to the wt:molar concentrations taught by Martin et al., or as shown in the preceding discussion, converts the weight to molar concentrations taught by Martin et al. to the wt:wt format used in claim 1, the end result is the same: the ratios taught by Martin et al. and the ratios set forth in claim 1 are very different, and Martin et al. do not suggest the present invention.

It would not have been obvious from the cited references taken in combination to have made the complexes of the Applicants' invention. First, as noted above, Yu et al. gave no guidance on how an antibody would be attached to a liposome and mentioned only the possibility of attaching a monoclonal antibody, not an antibody fragment. They give no guidance on how one would so link the antibody–or even if, in fact, it could be done, much less whether or how one would link an scFv. Wang et al. teach only linking an antibody or antibody fragment to a toxin rather than to a liposome and that an scFv-

cys-linked toxin was less potent than the toxin linked to the full antibody. This would indicate that the full antibody is more useful than the scFv. Further, as also noted above, the ratios of scFv to toxin used by Wang et al, were very different from the ratios of scFv to liposome set forth in the present claims. Nilsson et al. disclosed a fusion protein scFv, not chemically conjugating an scFv through a sulfhydryl group at its 3' end, and they did not suggest any way in which the fusion protein scFv could be linked to a lipid vesicle. Martin et al. do not fill in these gaps, as they teach linking only an Fab, rather than an scFv and, as pointed out above, there are significant differences between an Fab and an scFv. One cannot simply substitute one for the other, as shown in the comparison of ratios set forth above. The ratios taught by Martin et al. would not work with an scFv antibody fragment. Furthermore, not only are the ratios taught by Wang et al. for the scFv : toxin and the ratios of taught by Martin et al. for the Fab : lipid vesicle very different from the presently claimed ratios for the scFv : liposome, the ratios of Wang et al. and Martin et al. are very different from one another. Thus, one of skill in the art considering these two papers together would have no guidance or direction for how to proceed when using an scFv-cys (from Wang et al.) with a liposome (from Martin et al.). Moreover, Wang et al. demonstrated that forming a protein-protein bond is very different from the protein-lipid binding of the present invention. As noted above, Wang et al. disclose that as the ratio of scFv to toxin increased from 1:1 to 1:2, the efficiency decreased from 70% to 40%. The is not what happens with the scFv-liposome complex of the present invention, as is shown by

the data presented in Xu, Liang, et al., *Molecular Cancer Therapeutics* 1:337-346 (2002), a copy of which is attached. Figures 3, 4a and 4b show, respectively, the efficient conjugation of scFv-cys to a cationic liposome and that the immunoreactivity of the scFv-cys is maintained following conjugation to a cationic liposome and following conjugation of that resultant immunoliposome with DNA.

As these data show, with the present invention, the efficiency does not decrease as the ratio of scFv to liposome increases. This clearly is an unexpected result in view of the prior art.

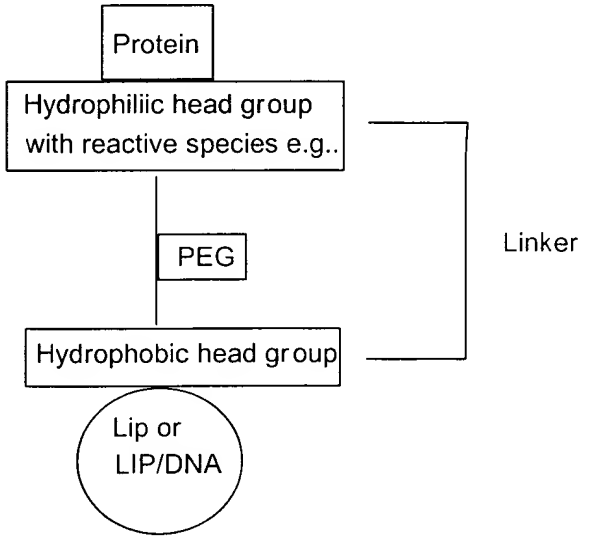
Applicants respectfully submit that it is only with the value of hindsight gleaned from the present application that one could find that the cited references suggest immunoliposomes comprising scFv antibody fragments. And furthermore, even if one were to assume, for the sake of argument, that the references do make such a suggestion, the references provide no practical guidance as they do not suggest what ratios could be useful to form a stable scFv-liposome complex with biological activity. As shown above, the ratios set forth in the references that might be used for guidance are of no help at all, as the ratios given are significantly different from the ratios found to be useful by the present inventors and set forth in claim 1. It would take an undue amount of experimentation to arrive at the complex and ratios set forth in claim 1 of the present application. Accordingly, the present invention is not obvious over the cited references.

Claims 1-4, 7, 8, 12, 69, 73 and 74 have been rejected under 35 U.S.C. § 103(a) as unpatentable over US 2004/0209366 (hereinafter the '336 application) in view of Wang et al., Martin et al. , Xu et al. *Human Gene Therapy* 467-475 (1997)) and U.S. Patent 6,200,956. The examiner asserted that the primary reference discloses the use of a targeting moiety, such as antibody fragments, linked to a cationic lipid nucleic acid complex (liposome and effector molecule, such as a nucleic acid encoding p53) and that the antibody fragment can be attached to the liposome before or after the formation of the nucleic acid: lipid complex. The examiner further asserted that the application teaches a w/w ratio of antibody fragment to lipid of 1 : 12.2, within the range recited in claim 1 of the present application, and that the reference teaches that the immunoliposomes of the invention could deliver a liposome - encapsulated anti-cancer drug to target cells. She acknowledged that the reference does not disclose covalently binding the scFv to DOPE linked to MPB nor the binding of scFv to transferrin receptor, with the nucleic acid molecule of interest encoding a wild type p53 as recited in dependent claims. In view of the teachings of the secondary references, however, the examiner asserted that it would have been obvious to have made a targeted immunoliposome that would be useful in delivering wild type p53 effector to various types of cancer, such as head and neck cancer as taught by Xu et al. by using a smaller molecule such as an scFv as the targeting moiety. This rejection is traversed.

The primary reference relied upon by the examiner in making this rejection is the '336 application, which focuses on attaching a protein or nucleic acid to lipidic

microparticles through a linker molecule comprising a hydrophilic domain and hydrophobic domain. Alternatively, or in addition, the nucleic acid component can be contacted with an organic polycation to produce a condensed or partially condensed nucleic acid. In contrast, the present invention does not require or use either a condensing agent or a hydrophilic polymer in complexing scFv to liposomes.

The only discussion in the '336 application of a complex between an scFv antibody fragment and a liposome is in Examples 5, 7, 10 and 12; the Detailed Description of the invention focuses on Fab fragments and only mentions scFv in passing in paragraph 0150. All four of the noted examples require the presence of a hydrophilic polymer (PEG) linker (Maleimido-propionylantido-PEG2000-diastearoylphosphatidylethanolamine (Mal-PEG-DSPE)). The linker attaches the scFv either by conjugation or by engineering the linker into the protein. The resultant complex is illustrated below:



Such complexes clearly are quite different from the complexes of the present invention, in which the scFv is directly conjugated to the liposome.

Furthermore, the examples do not teach or suggest the 1:5 to 1:40 w/w ratio of protein:lipid required by the claims of the present invention. Example 5 provides that the ratio of scFv to lipid was 0.35 mg scFv : 150 nmol lipid. This is equivalent to 1µg scFv : 0.489 nmol lipids. This ratio clearly is outside the range of antibody fragment : lipid of 1 µg : 7 nmol to 1 µg : 56 nmol scFv : lipid (converted from the w/w ratio range of 1:5 to 1:40 set forth in claim 1; see the discussion of the Wang et al. paper above for the conversions of the ratios). In Example 7, the ratio of antibody fragment to lipid is 15.6 µg : 1 µmol, which also clearly is outside the ratio of the present invention. Examples 10 and 12 refer back to Example 5.

The only teaching in the '336 application regarding the conjugation of scFv antibody fragments to liposomes, therefore, is that a polymeric linker is needed and that the ratio of fragment to lipid is very different from that of the Applicants' present invention. Furthermore, it should be noted that the '336 application only uses scFv in connection with binding to drugs, not to a nucleic acid. Thus, this reference clearly does not lead one to the present invention.

The four secondary references cited by the examiner do not compensate for the deficiencies of the '336 application. The shortcomings of the Wang et al. and Martin et al. references have been discussed above in connection with the previous ground of rejection, and that discussion is equally applicable here. Wang et al. only teaches conjugating an scFv to a toxin, rather than a lipid, and at a ratio well outside the protein to lipid ratio set forth in claim 1. Martin et al. focus on complexes with Fab' fragments, not scFv, and certainly give no indication that scFv fragments could be linked to liposomes, much less what ratios of such a fragment to liposome would be useful. As noted above, the ratio of Fab' : lipid used by Martin is very different from the ratio range found by Applicants to be suitable.

The third secondary reference cited by the examiner is a paper by Xu et al. In this reference, the authors discuss complexes in which liposomes are complexed with transferrin, not an scFv, as targeting ligand, by simple mixing rather than by chemical conjugation. Transferrin and an scFv, such as the transferrin receptor scFv used in examples of the present application, are very different molecules, with different sizes and very different functions. Transferrin is a molecule of about 80 kDa which transports iron; an scFv is an antibody fragment and much smaller than transferrin, about 28 kDa. One of ordinary skill in the art would not expect that one could be substituted for the other and the paper does not suggest such a substitution. Indeed, a simple substitution of antibody fragment for transferrin would not prove to be useful, as the ratios of the components in the two complexes found to be suitable are very different:

complex with transferrin:

DNA/liposome/transferrin = 1 µg/ 8 - 10nmol/ 10 - 15 µg

complex with TfRscFv:

DNA/liposome/TfRscFv = 1 µg/ 6 - 20nmol/ 0.11 - 2.86 µg

(the amount of TfRscFv is determined by converting µg : µg scFv : lipid to µg : nmol and calculating the range of protein at the 6-20 nmol liposome using the claimed TfRscFv : lipid range of 1:5 to 1: 40).

As shown above, the amounts of protein used in the two complexes is very different, and these differences are due, at least in part, to the different sizes and properties of the two proteins. This difference in optimal protein range illustrates that the ratio at which the complex will work *in vitro* and *in vivo* can vary greatly depending upon the type of protein used in the complex. Two different proteins are not interchangeable at the same ratio, and a significant amount of work can go into determining the proper ratio. It is not obvious that simply because one can make a useful complex with transferrin that a useful complex can be made with an scFv, a much smaller, totally different type of protein. This is especially true given that the claimed complexes with scFv are the result of direct chemical conjugation between the antibody fragment and the liposome; in the complexes comprising transferrin the protein attaches to the liposome through direct bond formation via simple mixing.

The fourth cited secondary reference is U.S. Patent 6,200,956 (hereinafter referred to as the '956 patent). This reference focuses on a method for condensing

DNA with a peptide (see column 2, lines 7-11, 26-33, 43-44 and 63, and column 3, lines 1-12). The reference does not teach the use of a ligand of any sort, and it does not even mention scFv. The reference does not give any guidance as to how one would attach a targeting element to their compound or at what ratio.

As has been explained above, different proteins and different ratios of protein to lipid are not interchangeable. Having a proper ratio is critical for the usefulness of the complex. The '956 patent provides no guidance on how adding a targeting element could influence charge ratio or the charge of the final compound for binding to cells. As the patentees do not teach using an scFv fragment in a complex with a liposome, they do not teach the direct conjugation of such fragments through a sulfur atom at the carboxy terminus of the fragments and they can provide no guidance on the useful ratio of antibody fragment to lipid or nucleic acid ligand to lipid. This reference thus does not compensate for any of the deficiencies of the other references cited by the examiner and the combined teachings of these references do not suggest the presently claimed invention.

In view of the foregoing amendments and discussion, applicants respectfully submit that the pending claims of the application are in condition for allowance.

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